Phase II Cancer Trials: When and How

NCIC CTG Course for New Investigators
August 9-12, 2011

Learning Objectives

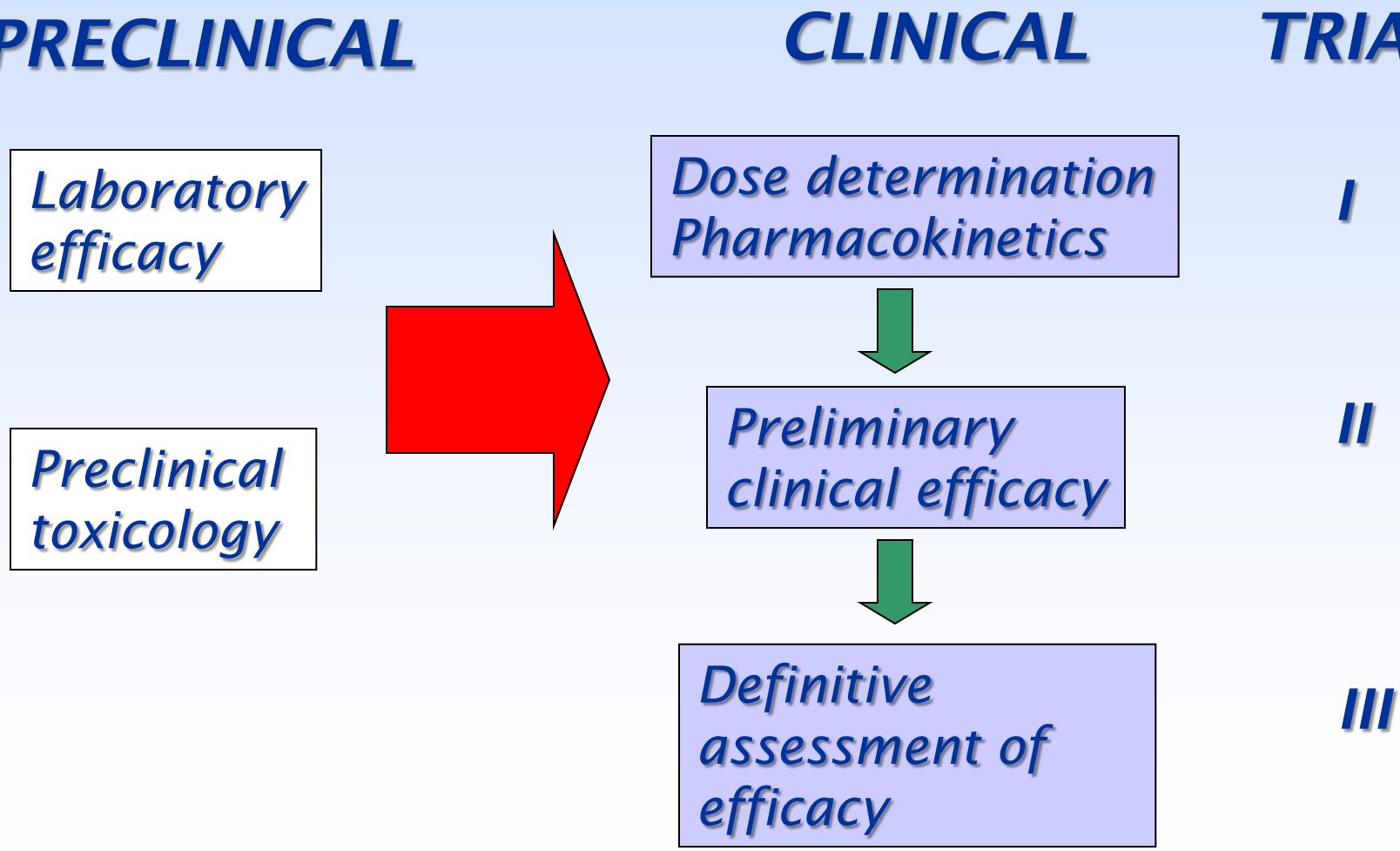
At the end of the session the participant should be able to

- Define the objectives of "screening" vs. "definitive" trials
- Describe the possible endpoints for phase II screening trials
- Understand basic concepts of phase II design including:
  - Non-randomized two-stage designs
  - Ha, Ho, alpha and beta errors in sample size determination
  - Types of randomized phase II design and their possible uses
- Understand the role of correlative studies within phase II screening trials
- Understand some of the controversial aspects of phase II designs for trials of molecular targeted agents.

Phase II Trials: Outline

- Role of phase II trials
- Objectives
- Endpoints
- Patient Population
- Design
- Special considerations:
  - Targeted
  - Randomized phase II trials
  - Correlative studies

Translation: From Laboratory Hypothesis to New Therapy



Examples: two new agents

Erlotinib

- EGFR tyrosine kinase inhibitor
- Oral phase I trial:
  - 150 mg po daily tolerable
  - toxicities: rash, diarrhea
- Question:
  - Does it show activity in **ovarian cancer**, a disease with high frequency of EGFR overexpression?

CCI-779

- mTOR inhibitor: theoretically of interest when PTEN loss
- IV phase I trial:
  - 25 mg IV weekly tolerable
  - toxicities : rash, mucositis
- Question:
  - Does it show activity in **endometrial cancer**, a disease with high frequency of PTEN mutation?

To Demonstrate Efficacy

- Screening trials – *does agent merit more study?*
  - Phase II studies
  - "Intermediate" endpoints (e.g. objective response)
- Definitive trials – *should this agent be adopted into practice?*
  - Phase III studies
  - Definitive, clinically meaningful endpoints (e.g. survival)

Objectives of Phase II Trials

- Primary:
  - To estimate level of anti-tumour activity of an agent or regimen in a given tumour type
- Secondary
  - To provide (further) information on toxicity
  - If applicable and possible, to generate hypotheses about relationship of features of drug target in tumours and response (or progression).

What are features of optimal *endpoint* for a *screening* trial?

1. Measures an effect on tumour
2. Standard definition of "effect"
3. Unlikely seen as part of natural history
4. Relatively early event
5. Experience shows *it can reliably identify drugs active in phase III*

Phase II endpoints: Options

1. Objective response (e.g. RECIST)
2. Minor response
3. Proportion non-progressive (non-PD rate)
4. Progression free survival
5. Tumour marker
6. Other biomarker
7. Functional Imaging
8. Some measure of "area under the curve" of maximal % change in tumour size.

Traditional Phase II endpoint: Objective Response

- Using this endpoint in *single agent* trials:
  - Does not require randomized design (since tumour shrinkage only rarely spontaneous)
  - Has been reasonably successful in identifying drugs that can improve survival

Standard Response Criteria

Varies by tumour type. Examples:

- *Most* Solid Tumours:
  - Objective response (e.g. RECIST 1.1)
- *Some* Solid Tumours:
  - CA125 response (Ovarian cancer)
  - PSA response (Prostate cancer)
  - MacDonald Criteria (Brain tumours)
- Hematololgical malignancies:
  - Lymphoma
  - IWG AML criteria

RECIST version 1.1 (Response Evaluation Criteria in Solid Tumors)

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,*], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]

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RECIST 1.1: Measuring Disease

- Measurable lesion:
  - ≥ 10 mm longest diameter on CT scan (assuming slice thickness 5 mm)
  - ≥ 15 mm shortest diameter for lymph node
- Up to 5 largest measurable lesions assessed (maximum 2 per organ site)
- Sum of diameters

RECIST 1.1: Defining Response

- Complete Response (CR):
  - Disappearance of all disease
- Partial Response (PR)
  - > 30% decrease in sum of diameters
- Progression (PD)
  - > 20% increase in sum of diameters and at least 5 mm absolute increase
- Stable disease (SD)
  - Neither PD nor PR.
- CR, PR must be confirmed ***if response primary endpoint***. SD has protocol defined "minimum" duration

Example of Marker Response: CA125 Response

- Gynecologic Cancer Intergroup criteria*:
  - Patient must have one baseline elevated sample (at least 2x ULN)
  - CA125 response if:
    - 50% fall from baseline
    - Confirmed by repeat sample at least 28 days later

*Rustin GJS et al J Natl Cancer Inst 96:487, 2004

Patient Population

- Patients to be enrolled in phase II trial should have characteristics which:
  - **Allow assessment of primary endpoint** in patients with disease of interest
  - Maximize the chance of seeing activity
  - Take into account drug toxicity and pharmacology

Examples: Population

CCI-779: Endometrium

- Measurable disease
- Performance status (ECOG) 0,1,2.
- No prior chemotherapy. One hormonal treatment allowed.

Erlotinib: Ovary

- Measurable disease; +/- CA125 > 2x ULN
- Able to swallow; no bowel obstruction
- One prior chemo regimen. Two cohorts will be studied:
  - > 6 mo
  - < 6 mo

Design

- Design should do two things:
  - Allow identification of **truly active drug** (i.e. limit the risk of a false negative result)
  - Limit the number of patients treated in case the drug is **truly inactive**.

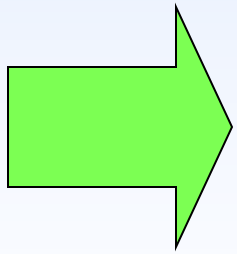
"Classic" Single Arm Design

- Multistage (usually 2-stage) non-randomized study.
- Sample size and stopping rule based on the level of activity (response rate) of interest (Ha) and the levels of the 2 key error rates:
  - The α error: false positive result
  - The β error: false negative result --- mostly we want to *minimize* this.

Statistical Design/Sample Size

- Several methods available:
  - Simon, Fleming, Gehan….
- Consult with statistician
- In general:

Smaller:
Response rate (Ha)
α value
β value



Larger:
Sample Size

Examples: Design

CCI-779: Endometrium

Ha **20%**

Ho **5%**

Enter 15 patients

- Close trial if no responses
- If ≥ 1 response: enroll 15 additional pts

If ≥ 4 /30 pts respond conclude agent is of interest for further study

α = 0.058; 1- β = 0.87

Erlotinib: Pt. Sens. Ovary

Ha **30%**

Ho **5%**

Enter 8 patients

- Close trial if no responses
- If ≥ 1 response: enroll 7 additional pts

If ≥ 3 /15 pts respond conclude agent is of interest for further study

α = 0.03; 1- β = 0.85

Platinum resistant: as at left

Reporting Results

- Account for all patients entered
- Describe:
  - Patient characteristics
  - Treatment delivery
  - Toxic effects
  - No. pts with: CR, PR, SD, PD
  - Response rate: based on all eligible patients (do not inflate response rate by reducing denominator)
  - Response Duration
  - Outcome of any "special" endpoint e.g. molecular marker

After Phase II is Complete:

- If a minimum level of activity seen further evaluation warranted:
  - Confirmatory phase II
  - Combination phase I/II – may be randomized
  - Randomized single agent studies
- If no responses, drug concluded to be of no interest for further study

Issues with "Traditional" Phase II

- What about…
  - Targeted anti-cancer drugs (so called non-cytotoxic agents) that may not cause tumour shrinkage in animals?

Era of Molecular Targeted Therapy: Phase II Trial Challenges

- Is response a realistic endpoint with molecular targeted agents?
- If not:
  - What are options of alternative endpoints?
  - What implications do use of non-response endpoints have on design?
- Should population be "enriched" for target expression?

Phase II endpoints: Options

1. Objective response (e.g. RECIST)
2. Minor response
3. Proportion non-progressive (non-PD rate)
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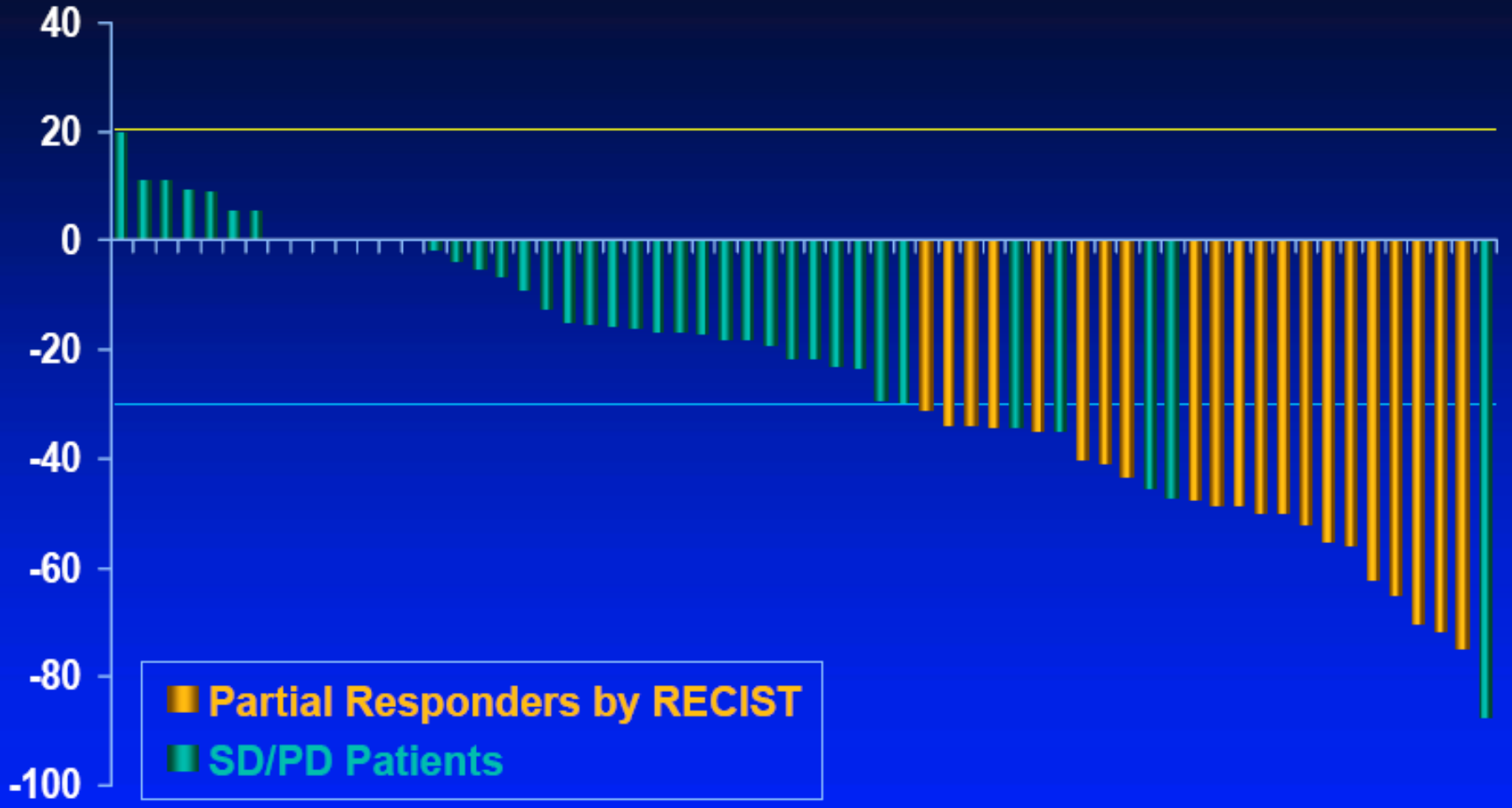
5. Tumour marker
6. Other biomarker
7. Functional Imaging
8. Some measure of "area under the curve" of maximal % change in tumour size.

SU11248 Maximum % Reduction of Target Lesions by Patient



Phase II endpoints: Options

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Require *randomized* designs

What alternative endpoints/designs have been used in Phase II screening trials of targeted agents?

- 19 targeted agents with single agent phase II reports in one of 6 common tumour types
- Describe endpoints, design used and whether results related to eventual phase III success
- Total: 89 trials found

El-Maraghi, Eisenhauer, JCO, 2008

Agents/Targets: Phase II Review

Target	Agent	#Reports
Angiogen-esis	ZD6474 SU5416 Bevacizumab SU11248	1 2 2 2
PKC alpha	ISIS 3521	5
raf kinase	BAY 43-9006 ISIS 5132	1 4
DNA MTase	MG98	1
MEK	CI-1040	1
mTOR	CCI-779	3

Target	Agent	#Reports
EGFR/ HER2	ZD1839 OSI-774 C225 trastuzumab	14 5 3 8
ckit/abl	STI571	7
MMP	Marimastat BMS-275291	1 1
Farnesyl trans-ferase	R115777 SCH66336	5 1

Results: Study Outcomes by Trial

Tumour Type	Number of trials with objective response rate as shown (%)				
	Not reported	0	>0 - ≤10	>10-≤20	>20
Breast	0	6	5	7	3
Colorectal	0	8	3	0	0
Lung	2	10	4	3	3
Ovary	0	3	3	0	0
Prostate	7	7	0	0	0
Renal	4	4	4	1	2
TOTAL (%)	13 (15)	38 (43)	19 (21)	11 (12)	8 (9)

Summary and Comparison of Cytotoxics with Targeted Agents Reviewed

Response rates (all trials)	No. Targeted Agents	No. Approved for ANY Tumour type Included in	%
>(			
1(			
>20	1	1	100
TOTAL	*19*	*7 (8)*	*32*

p = .005 (excluding gefitinib)
p < .0001 (including gefitinib)

Randomized Phase II Designs

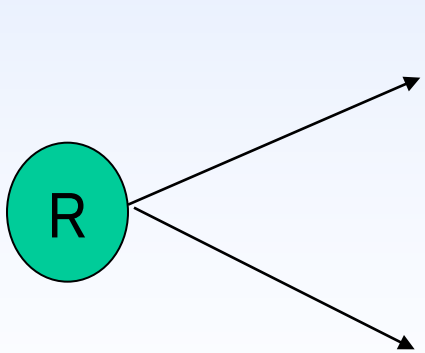
- Small sample size trials which are not adequately powered to compare outcomes.
- Endpoints can be response or other (e.g. PFS) depending on design and question being addressed
- Useful in several circumstances….

Examples:
Randomized Phase II Designs

- "Pick the Winner" Two schedules of a new drug look interesting. Randomized trial to select the schedule most likely to be best:

  e.g. IND.163

Patients:
Breast cancer
1 prior chemotherapy



RAD001 daily

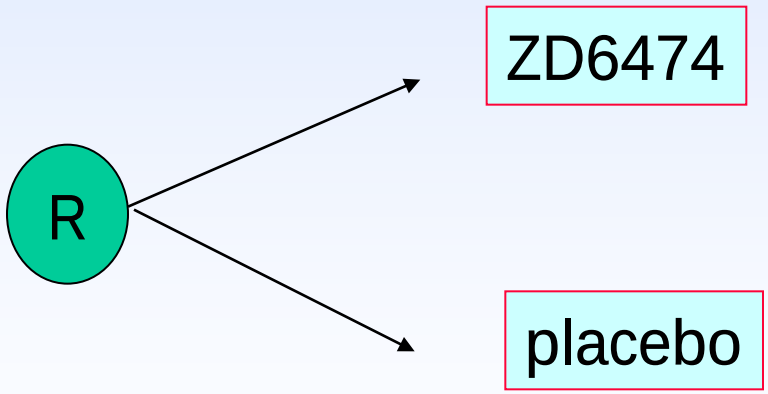
RAD001 weekly

Examples:
Randomized Phase II Designs

- Identify early evidence of effect: Standard vs. experimental regimen to identify sufficient activity to merit phase III.

  e.g. BR.20

Patients:
SCLC, Completed Rx with CR, PR



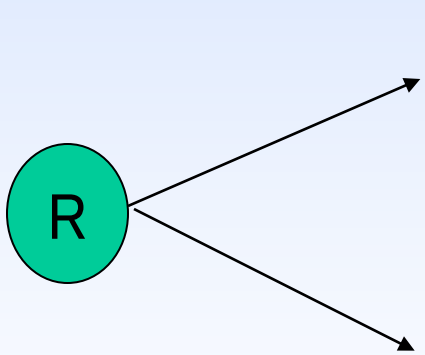
Primary endpoint: 2.5 mo improvement in PFS
Statistics: power 80%, one-sided alpha 0.1

Examples:
Randomized Phase II Designs

- Use control arm to interpret results:
  Control arm serves to help *interpretation of results* in experimental arm

  e.g. IND.165

Patients:
CRPC
No prior chemotherapy



Primary endpoint: PSA response rate

Statistics:

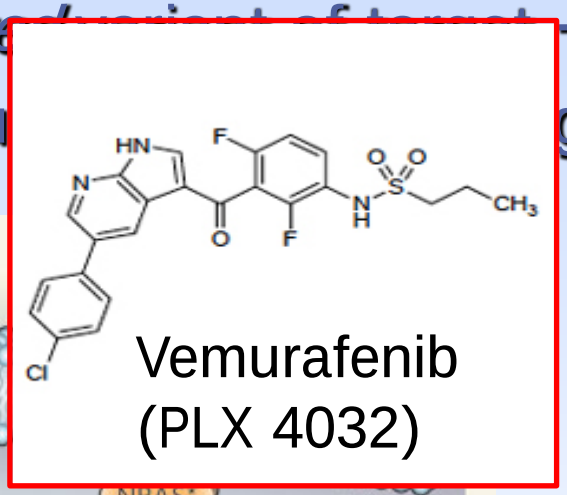
- H0 < 40%, H1 > 60%, α = 0.1, β = 0.1
- >20/40 pts in OGX-011 Arm with PSA resp of interest

Correlative Biology/Enrichment

- When to enrich for molecularly defined subset?
- What to enrich for?
- *Depends on how robust the preclinical data is on molecular predictor*
- *In all cases:* need tumour collection from all patients

An Easy Example

- Agent designed to inhibit *mutated variant of target* → select for patients having tumou get.



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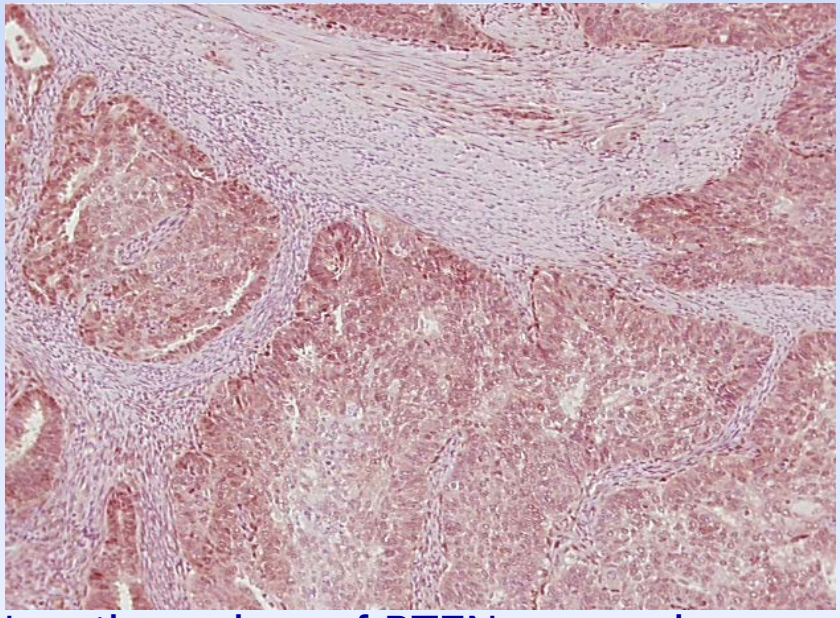
More Common Setting

- Agent affects *normal variant* of target(s)
- Most drugs affect several targets
- Phase II trial: opportunity to develop/refine *hypotheses* about which tumour subsets are most sensitive (or least insensitive)
- May be challenging – look for altered expression, mutations, amplifications in pathway and in salvage pathway

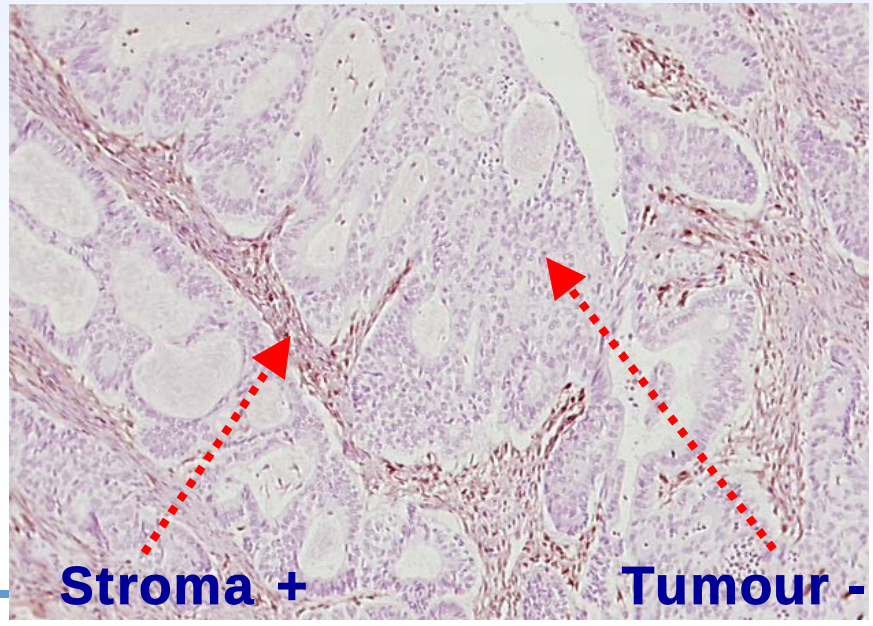
Example:

Phase II Single Agent Trial mTOR inhibitor in Endometrial ca

PTEN IHC positive = normal



Negative = loss of PTEN expression



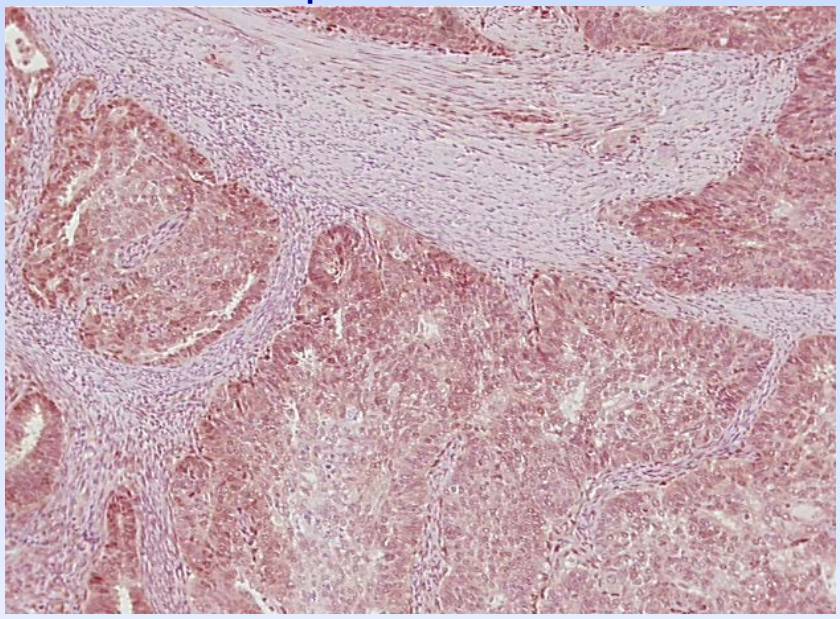
IND.160 A (Temsirolimus Endometrium)

Response	PTEN +ve	PTEN -ve
PR	3	1
SD	3	14
PD	3	2
IN		3
Total	9	20

No evidence PTEN loss needed for PR

Similar results pmTOR, pS6k

PTEN IHC positive = normal



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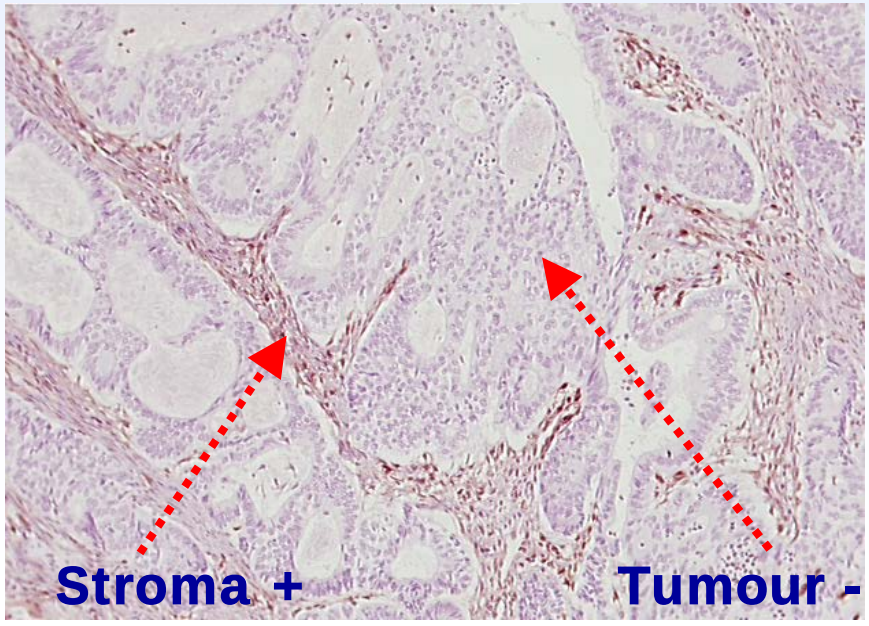

Mutational Analysis

Best Response Association Tested	Mutation type	P-value
PR vs. other	Any	1.0
	PIK3CA	0.4
	PIK3CA or Akt	1.0
PR + SD vs. other	Any	0.3
	PIK3CA	0.4
	PIK3CA or Akt	0.7
PD vs. other	Any	0.7
	PIK3CA	0.7
	PIK3CA or Akt	0.7

Lesson: It is challenging to find "THE" biomarker

- Phase II can be place to start but seldom where the story finishes
- Sample size is relatively small to do much more than generate/refine hypotheses

Summary: Phase II Trials

- Goal: Screen new agent/combination for activity.
- Primary Endpoints:
  - Single agent/single arm: Objective response
  - Randomized (single agent or combo): response or PFS
- Design:
  - Depends if single arm or randomized
  - Should minimize possibility of false negative outcome
- Correlative studies: Should be routine
  - At minimum: to generate hypotheses about selection biomarker
- Drugs active in phase II: Need further evaluation